CLAIMS

We claim:

1. A humanized, chimeric or human monoclonal antibody or antigen-binding portion thereof that specifically binds to insulin-like growth factor I receptor (IGF-IR).

2. The antibody or portion thereof according to claim 1, wherein the IGF-IR is human.

3. The antibody or antigen-binding portion thereof according to any one of claims 1 or 2, wherein the antibody or portion thereof has at least one property selected from the group consisting of:

a) does not bind to mouse, rat, dog or rabbit IGF-IR;

b) binds to cynomologous or rhesus IGF-IR but not to marmoset IGF-IR;

c) inhibits the binding of IGF-I or IGF-II to IGF-IR.

d) has a selectivity for IGF-IR that is at least 50 times greater than its selectivity for insulin receptor;

e) inhibits tumor growth *in vivo*;

f) causes IGF-IR disappearance from the cell surface when incubated with a cell expressing IGF-IR;

g) inhibits IGF-IR-induced tyrosine phosphorylation;

h) binds to IGF-IR with a K_d of 8×10^{-9} M or less; and

i) has an off rate for IGF-IR of K_{off} of 10^{-4} or smaller.

4. The antibody or antigen-binding portion thereof according to claim 3, wherein the antibody or portion thereof has all of said properties.

5. The antibody or antigen-binding portion thereof according to any one of claims 1 or 2, wherein the antibody or portion thereof has at least one property selected from the group consisting of:

a) cross-competes for binding to IGF-IR with an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

b) binds to the same epitope of IGF-IR as an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

c) binds to the same antigen as that bound by the antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

d) binds to IGF-IR with substantially the same K_d as an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3; and

e) binds to IGF-IR with substantially the same off rate as an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3.

6. The antibody or antigen-binding portion thereof according to claim 5, wherein the antibody or portion thereof comprises all of said properties.

7. The antibody or antigen-binding portion thereof according to any one of claims 1-6, wherein said antibody or portion thereof inhibits binding between IGF-IR and IGF-I or IGF-II with an IC_{50} of less than 100 nM.

8. The antibody or antigen-binding portion thereof according to any one of claims 1-7, wherein said antibody or antigen-binding portion thereof comprises a variable region of a κ light chain, wherein the sequence of said variable region of said κ light chain comprises no more than ten amino acid changes from the amino acid sequence encoded by a germline Vκ A30, A27 or O12 gene.

9. The antibody or antigen-binding portion thereof according to claim 8, wherein the variable region of the κ light chain comprises an amino acid sequence selected from the group consisting of the amino acid sequence of SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 18 and SEQ ID NO: 22, or an amino acid sequence having 1-10 amino acid insertions, deletions or substitutions therefrom.

10. The antibody or antigen-binding portion thereof according to any one of claims 1-7, wherein said antibody or antigen-binding portion thereof comprises

a variable region of a heavy chain, wherein the sequence of said variable region comprises no more than eight amino acid changes from the amino acid sequence encoded by a germline V_H DP47, DP35, DP71 or VIV-4 gene.

11. The antibody or antigen-binding portion thereof according to claim 10, wherein the variable region of the heavy chain comprises an amino acid sequence selected from the group consisting of the amino acid sequence of SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 12, SEQ ID NO:16, SEQ ID NO: 20 and SEQ ID NO: 24, or an amino acid sequence having 1-10 amino acid insertions, deletions or substitutions therefrom.

12. The antibody or antigen-binding portion thereof according to any one of claims 1-11 that is

a) an immunoglobulin G (IgG), an IgM, an IgE, an IgA or an IgD molecule, or is derived therefrom; or

b) an Fab fragment, an $F(ab')_2$ fragment, an F_v fragment, a single chain antibody, a humanized antibody, a chimeric antibody or a bispecific antibody.

13. The antibody or antigen-binding portion thereof according to any one of claims 1-12, wherein the antibody or portion thereof comprises an amino acid sequence of at least one CDR region from a variable region, wherein said variable region is selected from the group consisting of:

a) a variable region of the light chain of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

b) a variable region of a light chain comprising an amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 18 and SEQ ID NO: 22, or an amino acid sequence having 1-10 amino acid insertions, deletions or substitutions therefrom;

c) a variable region of the heavy chain of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3; and

d) a variable region of a heavy chain comprising an amino acid sequence selected from SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 12, SEQ ID

NO:16, SEQ ID NO: 20 and SEQ ID NO: 24, or an amino acid sequence having 1-10 amino acid insertions, deletions or substitutions therefrom.

14. The antibody or antigen-binding portion thereof according to claim 13, wherein the antibody or portion thereof comprises all of the amino acid sequences of the CDR regions a variable region, wherein said variable region is selected from the group consisting of selected from the group consisting of:

a) a variable region of the light chain of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

b) a variable region of a light chain comprising an amino acid sequence selected from SEQ ID NO: 2, SEQ ID NO: 6, SEQ ID NO: 10, SEQ ID NO: 14, SEQ ID NO: 18 and SEQ ID NO: 22, or an amino acid sequence having 1-10 amino acid insertions, deletions or substitutions therefrom;

c) a variable region of the heavy chain of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

d) a variable region of a heavy chain comprising an amino acid sequence selected from SEQ ID NO: 4, SEQ ID NO: 8, SEQ ID NO: 12, SEQ ID NO:16, SEQ ID NO: 20 and SEQ ID NO: 24, or an amino acid sequence having 1-10 amino acid insertions, deletions or substitutions; and

e) the variable regions of the light chain and the heavy chain of an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3.

15. The antibody according to claim 1, wherein the antibody is selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3.

16. The antibody according to claim 1, wherein said antibody comprises a heavy chain and a light chain, and wherein the amino acid sequences of the light chain and heavy chain are selected from the group consisting of:

a) the amino acid sequence of the heavy chain and the amino acid sequence of the light chain of 2.12.1;

b) the amino acid sequence of the heavy chain and the amino acid sequence of the light chain of 2.13.2;

c) the amino acid sequence of SEQ ID NO: 45 and the amino acid sequence of SEQ ID NO: 47; and

d) the amino acid sequence of SEQ ID NO: 49 and the amino acid sequence of SEQ ID NO: 51.

17. The antibody according to claim 1, wherein said antibody has an amino acid sequence comprising the amino acid sequences of the CDRs of antibodies 2.12.1 or 2.13.2, or CDRs of that antibody having no more than 5 conservative amino acid changes.

18. A pharmaceutical composition comprising the antibody or portion thereof according to any one of claims 1-17 and a pharmaceutically acceptable carrier.

19. The pharmaceutical composition according to claim 18, further comprising an antineoplastic, chemotherapeutic or anti-tumor agent.

20. A process for making an antibody that binds to IGF-IR, comprising the steps of:

a) immunizing a non-human mammal with an immunogen comprising IGF-IR, wherein the mammal is capable of expressing human antibodies in B cells of the animal;

b) isolating B cells from the mammal;

c) screening said B cells, or cell lines derived therefrom, to identify a cell line that produces antibodies that bind to IGF-IR;

d) culturing the cell line that expresses antibodies that bind to IGF-IR; and

e) isolating antibodies that bind to IGF-IR from the cell line.

21. An isolated cell line that produces the antibody according to any one of claims 1-17.

22. The cell line according to claim 20 that produces an antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3, or wherein the antibody has the same amino acid sequences thereof.

23. A method of diagnosing the presence or location of an IGF-IR-expressing tumor in a subject in need thereof, comprising the steps of

a) injecting the antibody according to any one of claims 1-17 into the subject,

b) determining the expression of IGF-IR in the subject by localizing where the antibody has bound,

c) comparing the expression in part (b) with that of a normal reference subject or standard, and

d) diagnosing the presence or location of the tumor.

24. A method of treating cancer in a human with an antibody or antigen-binding portion thereof that specifically binds to IGF-IR, comprising the step of administering to the human an amount of the antibody effective to treat said cancer.

25. A method of treating a patient in need thereof with the antibody or antigen-binding portion thereof according to any one of claims 1-17, comprising the step of administering to the patient an effective amount of the antibody.

26. The method according to either of claims 24 or 25, further comprising the step of administering an anti-neoplastic, anti-tumor, anti-angiogenic or chemotherapeutic agent.

27. An isolated nucleic acid molecule that comprises a nucleic acid sequence that encodes a heavy chain or antigen-binding portion thereof or a light chain or antigen-binding portion thereof of an antibody according to any one of claims 1-17.

28. The isolated nucleic acid molecule according to claim 27, wherein the nucleic acid molecule comprises a nucleic acid sequence selected from the group consisting of:

a) a nucleic acid sequence encoding at least one CDR region from the heavy chain of the antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

b) a nucleic acid sequence encoding the three CDR regions from the heavy chain of the antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

c) a nucleic acid sequence encoding the amino acid sequence of the heavy chain or the antigen-binding portion thereof of the antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

d) a nucleic acid sequence encoding at least one CDR sequence from the light chain of the antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

e) a nucleic acid sequence encoding the three CDR sequences from the heavy chain of the antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

f) a nucleic acid sequence encoding the amino acid sequence of the light chain or the antigen-binding portion thereof of the antibody selected from the group consisting of 2.12.1, 2.13.2, 2.14.3, 3.1.1, 4.9.2 and 4.17.3;

g) a nucleic acid sequence encoding the amino acid sequence of selected from the group consisting of SEQ ID NOS: 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 and 22; and

h) a nucleic acid sequence selected from the group consisting of SEQ ID NOS: 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 23;

wherein said nucleic acid molecule optionally comprises a nucleic acid sequence encoding the amino acid sequence of SEQ ID NO: 28 or SEQ ID NO: 26.

29. A vector comprising the nucleic acid molecule according to either of claims 27 or 28, wherein the vector optionally comprises an expression control sequence operably linked to the nucleic acid molecule.

30. A host cell comprising the vector according to claim 29 or the nucleic acid molecule according to either of claims 27 or 28.

31. A method of making an anti-IGF-IR antibody or antigen-binding portion thereof, comprising culturing the host cell according to claim 30 or the cell line according to claim 21 under suitable conditions and recovering said antibody or antigen-binding portion.

32. A non-human transgenic animal comprising the nucleic acid according to either of claims 27 or 28, wherein the non-human transgenic animal expresses said nucleic acid.

33. A method of treating a subject in need thereof with an antibody or antigen-binding portion thereof that specifically binds to IGF-IR, comprising the steps of

(a) administering an effective amount of an isolated nucleic acid molecule encoding the heavy chain or the antigen-binding portion thereof, an isolated nucleic acid molecule encoding the light chain or the antigen-binding portion thereof, or both the nucleic acid molecules encoding the light chain and the heavy chain or antigen-binding portions thereof; and

(b) expressing the nucleic acid molecule.